

Milk and Dairy Product Consumption and Bladder Cancer Risk: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Some studies have reported that milk and dairy product consumption reduces bladder cancer incidence, whereas others have reported null or opposite findings. This meta-analysis of 26 cohort and case-control studies has been conducted to pool the risk of the association between milk and dairy products and bladder cancer. A systematic search in MEDLINE, EMBASE, and the Web of Science (from inception to 30 April 2018) was conducted. Random-effects models were used to compute pooled estimates of RR for high or medium compared with low consumption of milk and dairy. Sensitivity analyses were conducted. Subgroup analyses were performed based on type of dairy, gender, geographic location, and type of study design. Random-effects meta-regression was used to evaluate other confounding factors. Overall, medium compared with low consumption was associated with lower pooled risk of bladder cancer for total dairy products (RR = 0.90; 95% CI: 0.81, 0.98), milk (RR = 0.90; 95% CI: 0.82, 0.98), and fermented dairy products (RR = 0.87; 95% CI: 0.79, 0.96). The inverse association for milk consumption was stronger in Asians (RR = 0.79; 95% CI: 0.59, 0.98) and in cohort design studies (RR = 0.85; 95% CI: 0.71, 0.99). Moreover, high compared with low consumption was significantly associated with a lower pooled risk for milk (RR = 0.89; 95% CI: 0.81, 0.98) and fermented dairy products (RR = 0.78; 95% CI: 0.61, 0.94). However, high compared with low consumption of whole milk was significantly associated with a higher risk (RR = 1.21; 95% CI: 1.04, 1.38). The statistical heterogeneity was considerable. In conclusion, the present meta-analysis suggests a decreased risk of bladder cancer associated with medium consumption of total dairy products and with medium and high consumption of milk and fermented dairy products. An increased risk of bladder cancer was observed with high consumption of whole milk. Interpretations of the results should be made with caution. This review was registered at www.crd.york.ac.uk/prospero as CRD42018097020. *Adv Nutr* 2019;10:S224–S238.

Keywords: milk, dairy products, fermented dairy products; whole milk; bladder cancer, meta-analysis; systematic review

Introduction

According to the International Agency for Research on Cancer, bladder cancer is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012 (3% of all new cases of cancer) (1).

Bladder cancer becomes more common with increased age and is more common in men than in women. Moreover, the most common risk factor for developing bladder cancer is cigarette smoking. Smokers are 4–7 times more likely to develop bladder cancer than nonsmokers. Other important risk factors are the following: exposure to aromatic amines and 4,4'-methylenebis (2-chloroaniline) used in different types of industries (textile, print, paint, etc.), schistosomiasis parasitic disease, exposure to arsenic in drinking water, certain medications (phenacetin, cyclophosphamide, and chlornaphazine), radiation, and genetic factors (2). However,

the occurrence of bladder cancer has not been fully explained by these risk factors. Although the evidence is inconsistent or controversial, dietary habits could also influence the risk of bladder cancer because most metabolites are excreted through the urinary bladder (3).

With regards to dietary factors, different studies have suggested a protective effect of fruit and vegetable intake against bladder cancer and a possible positive association with fat intake (4). The relation between the consumption of milk or dairy products and the risk of bladder cancer has been investigated in several epidemiologic studies since 1980. Some studies have reported that higher intakes of milk or dairy products reduce bladder cancer incidence, whereas other studies observed no significant association. In 2011, the findings of a meta-analysis by Li et al. (5) were not supportive of an independent relation between the

intake of milk or dairy products and the risk of bladder cancer, with the exception of inverse associations found in the United States for bladder cancer risk and milk intake and in Japan for bladder cancer risk and dairy product intake. Another meta-analysis conducted in 2011 by Mao et al. (6) suggested a potential protective effect of milk for bladder cancer, but this relation varied widely across geographical regions and specific dairy products. Specifically, they noted a significant association of higher milk consumers with decreased risk of bladder cancer only in Asia and postulated that the different observation may be explained, at least in part, by the variations of milk consumption across the world (6). However, conclusions of these 2 meta-analyses (5, 6) were consistent regarding their findings being based on limited research and future research to confirm these findings is warranted. According to these results, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) in their Continuous Update Project Expert Report 2018 (Diet, nutrition, physical activity and bladder cancer) (7) concluded that the evidence of a higher consumption of milk and dairy products decreasing the risk of bladder cancer is limited.

Regarding the inconsistent findings on the relation between milk or dairy product intake and bladder cancer risk, this new meta-analysis of prospective cohort and case-control studies was conducted to address this topic and included 3 additional published observational studies. The main goal was to estimate the summary RR of the association between milk and dairy products and bladder cancer and examine potential sources of heterogeneity across studies. Specifically, more detailed analyses were conducted to clarify the relation between milk or dairy product intake and bladder cancer risk, taking into account the type of dairy products, fat content, quantity consumed, geographic location, and the type of study design.

Methods

This study was reported according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements (8) and followed the recommendations of the Cochrane Collaboration Handbook (9). This systematic review and meta-analysis was registered through the international prospective register of systematic reviews (PROSPERO) as CRD42018097020.

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Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/advances/>.

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Search strategy

We systematically searched the MEDLINE (via PubMed), EMBASE, and Web of Science databases from their inception until April, 2018. Observational studies addressing the association between dairy product consumption and bladder cancer were eligible. The search terms used for the search strategy were: "bladder cancer," "bladder-cancer," "bladder," "urinary tract cancer," "urinary bladder," "cancer," "dairy," "milk," "yogurt," "cheese," "kefir," "butter," "dairy products," "cohort study," "population-based," "case-control study," "prospective," and "case control." The literature search was complemented by screening references included in the articles considered eligible for the systematic review.

Study selection

Inclusion criteria were as follows: 1) participants: adult population; 2) study design: cohort studies or case-control studies with prospective or retrospective data collection; 3) exposure: dairy products [total, milk, (whole milk, low-fat milk, skimmed milk), fermented (i.e., yogurt, fermented milk products, yakult, quark, buttermilk, or sour cream), cheese, or butter] considered as reported by included studies; and 4) outcome: bladder cancer. The criteria for excluding studies were as follows: 1) reports not written in English or Spanish; 2) studies including individuals younger than 18 y old; and 3) ineligible publication types, such as review articles, editorials, comments, guidelines, or case-reports.

When >1 study provided data from the same sample, we only considered the one presenting the most detailed results or providing data for the largest sample size. However, data regarding sample characteristics were extracted from multiple reports to obtain the most complete information.

The literature search was performed independently by 2 reviewers (IC-R and LMB) and disagreements were solved by consensus or involving a third researcher (CS or BL-P).

Data extraction and quality assessment

The following data were extracted from the original reports: 1) year of publication; 2) study characteristics (country, period of data collection, and length of follow-up), 3) sample characteristics (sample size and age distribution), 4) dietary assessment, 5) dairy product assessed, 6) number of bladder cancer events, and 7) methodological quality. Information for case-control and cohort studies was extracted and organized separately into 2 tables.

The Quality in Prognosis Studies tool was used to evaluate the risk of bias in 6 domains: study participation (sampling bias), study attrition (attrition bias), prognostic factor measurement, outcome measurement (ascertainment bias), study confounding, and statistical analysis and reporting (10). Studies were considered to have a low, moderate, or high risk of bias if they satisfied 5–6, 3–4, or 1–2 of the 6 domains, respectively.

Data extraction and quality assessment were independently performed by 2 researchers (IC-R and LMB) and inconsistencies were solved by consensus or involving a third researcher (CS).

Statistical analysis and data synthesis

The lowest (the first quantile reported), medium (quantiles reported between the first and last quantiles), and highest (the last quantile reported) dairy product consumption categories reported from studies were considered as “low,” “medium,” and “high” dairy product consumption, respectively. The DerSimonian and Laird random-effects method was used to compute pooled estimates of RRs and their respective 95% CIs for the risk of bladder cancer associated with dairy product consumption (11). Forest plots were performed separately for high compared with low and medium compared with low dairy product consumption. The heterogeneity of results across studies was evaluated using the I^2 statistic (12), and the results were considered as: might not be important (0–40%), may represent moderate heterogeneity (30–60%), may represent substantial heterogeneity (50–90%), and considerable heterogeneity (75–100%) (9). In addition, the corresponding P values were considered.

When a study reported several statistical models, only the one including the largest number of additional covariates was considered. In addition, when studies reported ORs, the RR was calculated using the following equation: $RR = OR / (1 - \text{Prevalence}) + (\text{Prevalence} \times OR)$.

Sensitivity analyses were conducted excluding studies one by one from the pooled effect to assess the robustness of the summary estimates and to detect if any particular study accounted for a large proportion of the heterogeneity.

Subgroup analyses were performed based on the type of dairy products to estimate the risk of bladder cancer associated with dairy product consumption (total dairy products, milk, whole milk, fermented dairy products, cheese, and butter). In addition, subgroup analyses were performed based on gender, geographic location (Americas, Europe, and Asia), and type of study design (case-control and cohort studies) for each dairy product subgroup. Subgroup analyses were performed with ≥ 3 studies in each subgroup.

In addition, random-effects meta-regression was used to evaluate whether results differed according to the age of participants, percentage of current smokers, or the year when the study started, as these could be considered to be sources of heterogeneity. Random-effects meta-regressions were performed only in dairy product subgroups in which >10 studies were included (13).

Finally, publication bias was evaluated through visual inspection of funnel plots, as well as by using the method proposed by Egger et al. (14). Statistical analyses were performed using StataSE software, version 15 (StataCorp).

Results

Systematic review

From the 55 full-text articles reviewed, 26 studies [18 case-control (15–32) and 8 cohort studies (33–40)] met the eligibility criteria (Figure 1). The studies were conducted in 8 European countries, 10 countries in the Americas,

and 8 Asian countries. The reports were published between 1988 and 2014. Eight studies used a prospective design and 18 utilized a retrospective design. The beginning of data collection in the studies was established between 1942 and 2005 (Tables 1 and 2).

The age of included participants ranged between 18.0 and 99.0 y old, with sample sizes ranging from 200 to 233,236 participants; 595,698 participants were included in the meta-analysis (18,752 from case-control studies and 576,946 from cohort studies). The number of bladder cancer events observed were between 40 and 1586 across the studies. Most of the studies measured dairy product consumption with an FFQ, 4 studies used an interview, and 4 studies used a nonspecified dietary questionnaire (dairy product items considered in the dietary assessments in the studies are reported in Supplemental Table 1). The dairy products reported were: total dairy products, milk, cheese, butter, yogurt, cream, and 1 fermented milk (yakult). One study considered cocoa milk and pudding as dairy products in dietary assessments (39). Most of the studies reported data by categories of dairy product consumption, and only 1 study reported a dose-response analysis of dairy product consumption.

The studies included in the systematic review and meta-analysis presented approximate mean values of milk consumption as follows: low, ~ 50 mL/d (~ 4 mL/d in Asia, ~ 57 mL/d in the United States, and ~ 83 mL/d in Europe); medium, ~ 227 mL/d (~ 107 mL/d in Asia, ~ 229 mL/d in the United States, and ~ 306 mL/d in Europe); and high, ~ 336 mL/d (~ 200 mL/d in Asia, ~ 348 mL/d in the United States, and ~ 452 mL/d in Europe). The approximate mean values of whole milk consumption were low, ~ 0 mL/d; medium, ~ 110 mL/d; and high, ~ 220 mL/d. Moreover, for fermented dairy products, the approximate mean values were low, ~ 4 g/d (~ 8.3 g/d in Asia and ~ 0.0 g/d in Europe); medium, ~ 67 g/d (~ 36 g/d in Asia and ~ 94 g/d in Europe); and high, ~ 160 g/d (~ 71 g/d in Asia and ~ 249 g/d in Europe). Finally, for total dairy products, the approximate mean values were low, ~ 201 g/d (~ 16 g/d in Asia and ~ 304 g/d in Europe); medium, ~ 345 g/d (~ 92 g/d in Asia and ~ 515 g/d in Europe); and high, ~ 545 g/d (~ 195 g/d in Asia and ~ 779 g/d in Europe).

All studies reported models adjusted for several covariates. All studies reported models adjusted by age and most studies included sex and smoking status. Other common adjustments were residence and other food groups. No study included calcium supplement consumption in the adjustments.

Study quality

As assessed by the Quality in Prognosis Studies tool (Supplemental Table 2), 58% of the studies obtained a total score corresponding to a low risk of bias, 23% had a moderate risk of bias, and only 19% had a high risk of bias. The study attrition domain showed a moderate or high risk of bias in most studies (65%). Conversely, 85% of the studies showed a low risk of bias in the statistical analysis and

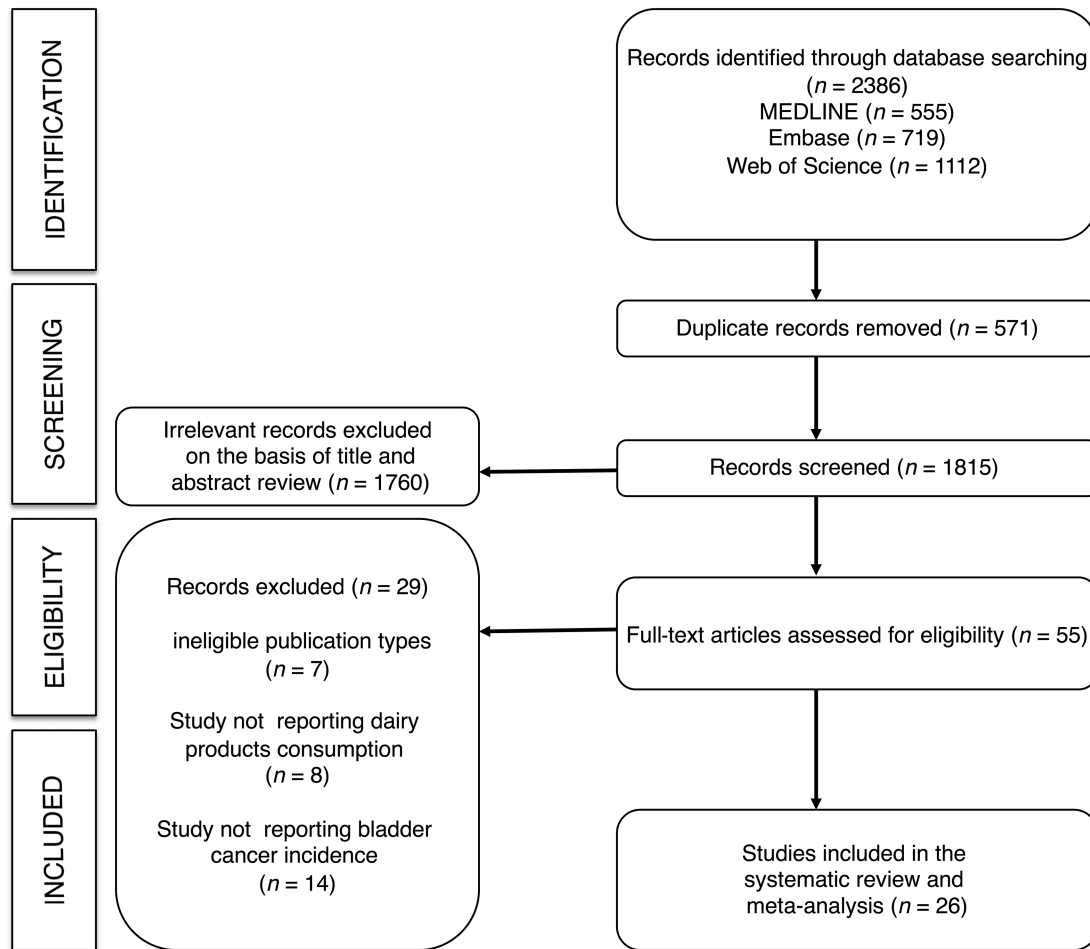


FIGURE 1 Flow diagram illustrating the identification and selection of studies.

reporting domain. No study scored a high risk of bias in the outcome measurement or statistical analysis and reporting domains.

Meta-analyses

For total dairy products, medium compared with low consumption was significantly associated with a lower pooled risk estimate for bladder cancer (RR = 0.90; 95% CI: 0.81, 0.98); the same was true for milk (RR = 0.90; 95% CI: 0.82, 0.98) and fermented dairy products (RR = 0.87; 95% CI: 0.79, 0.96). Heterogeneity in the RR estimates was not significant for dairy products ($I^2 = 47.0\%$; $P = 0.110$) or for fermented dairy products ($I^2 = 0.0\%$; $P = 0.539$) and was moderate for milk ($I^2 = 57.9\%$; $P = 0.004$) (Figure 2). Moreover, high compared with low consumption was significantly associated with a lower pooled risk estimate for bladder cancer for milk (RR = 0.89; 95% CI: 0.81, 0.98) and for fermented dairy products (RR = 0.78; 95% CI: 0.61, 0.94). However, high compared with low consumption was significantly associated with a higher pooled risk estimate for bladder cancer for whole milk (RR = 1.21; 95% CI: 1.04, 1.38). Heterogeneity in the RR estimates was moderate for fermented dairy products

($I^2 = 53.5\%$; $P = 0.072$) and substantial for milk ($I^2 = 66.4\%$; $P < 0.001$) and whole milk ($I^2 = 86.1\%$; $P < 0.001$) (Figure 3).

Sensitivity analysis

When the impact of individual studies was examined by removing studies from the analysis 1 at a time, a significantly higher risk of bladder cancer associated with medium compared with low whole milk consumption was found after removing the Ronco et al. study (32). Conversely, the significantly lower risk of bladder cancer associated with medium compared with low milk consumption disappeared after removing the Hemelt et al. (29), Mettlin et al. (18), and Wilkens et al. (20) studies. Finally, for medium compared with low and for high compared with low cheese consumption, a significantly lower risk of bladder cancer was found after removing the Brinkman et al. (30) and Keszei et al. (39) studies.

Subgroup analyses and meta-regression

When analyses were performed based on gender, geographic location, and type of study design, there were enough studies

TABLE 1 Characteristics of the case-control studies included in the systematic review and meta-analysis of the relation between dairy product intake and bladder cancer in the adult population¹

Reference	Country	Study/period of data collection (y)	Age distribution (y)	Sample size	Dietary assessment	Dairy products	Dairy amount comparison	Number of bladder cancer events	Variables of adjustment	Risk of bias ²
Mettlin and Graham (15)	United States	1957–1965	NA	1594	Interview	Milk	Servings per day (5 categories)	569	Age	Low
Risch et al. (16)	Canada	1979–1982	35–79	1618	Questionnaire	Milk	Servings per day (2 categories)	826	Age, sex, area of residence, lifetime smoking consumption, and history of diabetes	High
Slattery et al. (17)	United States	1977–1982	21–84	1308	Interview	Milk	Servings per week (4 categories)	419	Age, sex, smoking status, diabetes, and bladder infection	High
Mettlin et al. (18)	United States	1982–1990	18–97	1478	Questionnaire	High-fat milk 2% fat milk Low-fat milk	Servings per day (3 categories)	178	Age, sex, smoking history, education, and county of residence	Low
Riboli et al. (19)	Spain	1985–1986	<80	1224	Dietary questionnaire	Dairy Butter/cream	Quartiles of intake	432	Age, sex, smoking, area of residence, total calories	Moderate
Wilkens et al. (20)	United States	1977–1986	30–93	783	FFQ/32 items	Milk	Tertiles of intake	261	Age, smoking status, pack-years, employment in a high-risk occupation, consumption of dark green vegetables in men, and total vitamin C	High
Lu et al. (21)	Taiwan	1996–1997	67.5	200	FFQ	Milk	Nonintake vs intake	40	consumption in women Age, sex, date of admission, family history, ethnicity, and smoking status	Moderate
Wakai et al. (22)	Japan	1996–1999	20–99	592	FFQ/97 items	Dairy	Quartiles of intake	297	Age, sex, smoking, and occupational history as a cook	Low
Balbi et al. (23)	Uruguay	1998–1999	40–89	720	FFQ/64 items	Dairy Cheese Butter	Tertiles of intake	144	Age, BMI, calories	Moderate
Ohashi et al. (24)	Japan	1997–1998	49–80	625	Questionnaire	High-fat milk Fermented dairy Yakult	Servings per day (3 categories)	180	Age, sex, and smoking	Low
Radosavljević et al. (25)	Serbia	1997–1999	26–81	260	FFQ	High-fat milk Low-fat milk Yogurt	Nonintake vs intake	130	Age, sex, smoking, place of residence	Low

(Continued)

TABLE 1 (Continued)

Reference	Country	Study/period of data collection (y)	Age distribution (y)	Sample size	Dietary assessment	Dairy products	Dairy amount comparison	Number of bladder cancer events	Variables of adjustment	Risk of bias ²
Wakai et al. (26)	Japan	1994–2000	20–79	744	FFQ	Milk	Quartiles of intake	124	Age, sex, cumulative consumption of cigarettes, year of first visit	Low
Jiang et al. (27)	United States	1987–1999	25–64	3172	Interview	Milk	Quartiles of intake	1586	Age, sex, race, level of education, use of nonsteroidal anti-inflammatory drugs, carotenoid intake, number of years as hairdresser/barber, cigarette smoking status, duration of smoking, and intensity of smoking	Low
La Vecchia et al. (28)	Italy	1985–1987	45–74	344	FFQ	Milk Cheese Butter	Tertiles of intake	163	Age and sex	Moderate
Hemelt et al. (29)	China	2005–2008	65	824	Interview	Milk	Nonintake vs: - Intake - < Daily or daily - 1 cup or > 1 cup	432	Age, sex, smoking status, smoking frequency, and duration-adjusted ORs	Low
Brinkman et al. (30)	Belgium	1999–2004	50–80	575	Validated FFQ/322 items	Milk Cheese	Tertiles of intake	198	Sex, age, smoking status, number of cigarettes smoked per day, number of years smoking, occupational exposure to polycyclic aromatic hydrocarbons or aromatic amines, and energy intake	Low
Isa et al. (31)	China	2005–2008	40–80	956	FFQ/35 items	Dairy	Servings per week (5 categories)	487	Sex, age, smoking status, smoking duration, smoking amount, and other food groups	Low
Ronco et al. (32)	Uruguay	1996–2004	30–89	1735	FFQ/64 items	Milk Butter Cheese	Tertiles of intake	225	Age, residence, education, BMI, smoking, alcohol drinking, meat consumption, total energy, and total vegetable and fruit intakes	Low

¹NA, not available; PAH, polycyclic aromatic hydrocarbon.

²Risk of bias assessed using the Quality in Prognosis Studies (QUIPS) tool.

TABLE 2 Characteristics of cohort studies included in the systematic review and meta-analysis of the relation between dairy product intake and bladder cancer in the adult population¹

Reference	Country	Study/period of data collection (y)	Age distribution (y)	Sample size	Dietary assessment	Dairy products	Dairy amount comparison	Number of bladder cancer events	Variables of adjustment	Risk of bias ²
Ursin et al. (33)	Norway	1967–1978	35–74	15,914	Dietary questionnaire	Milk	Servings per day (3 categories)	91	Age, smoking, and residence	High
Chyou et al. (34)	United States	1942–1968	49–68	7995	FFQ/17 items	Milk Ice cream	Servings per week (3 categories)	96	Age and smoking	High
Michaud et al. (35)	United States	1986–1996	40–75	47,909	FFQ/131 items	Milk	Increase of 240 mL	252	Age, vegetables, smoking, energy, geographic region, fruits, and other beverages	Low
Nagano et al. (36)	Japan	Life-Span study/1979–1993	50–80	38,540	FFQ/22 items	Milk Butter/cheese	Servings per day (3 categories)	114	Age, BMI, gender, radiation, smoking, calendar time, and education	Moderate
Sakauchi et al. (37)	Japan	JACC study/1988–1997	40–79	65,184	FFQ/32 items	Milk Yogurt Cheese Butter	Servings per week (3 categories)	115	Sex, age, and smoking index	Moderate
Larsson et al. (38)	Sweden	Swedish mammography cohort/1987–1997	45–83	82,002	FFQ/96 items	Dairy Cheese Milk	Quartiles of intake	485	Age, smoking, sex, total energy intake, and education	Low
Keszei et al. (39)	Netherlands	Netherlands cohort study/1986–2002	55–69	120,852	Validated FFQ	Fermented dairy Dairy Nonfermented dairy Fermented dairy Cheese Butter Milk	Quintiles of intake	1549	Age, sex, smoking, fat, energy, meat, fruits, vegetables, and beverages	Low
Ros et al. (40)	Europe	EPIC/1992–2000	53.3	233,236	FFQ	Butter Milk	Tertiles of intake	513	Age, sex, smoking status, duration of smoking, lifetime intensity of smoking, energy intake from fat and nonfat sources	Low

¹JACC, Japan Collaborative Cohort; EPIC, European Prospective Investigation into Cancer and Nutrition.²Risk of bias assessed using the Quality in Prognosis Studies (QUIPS) tool.

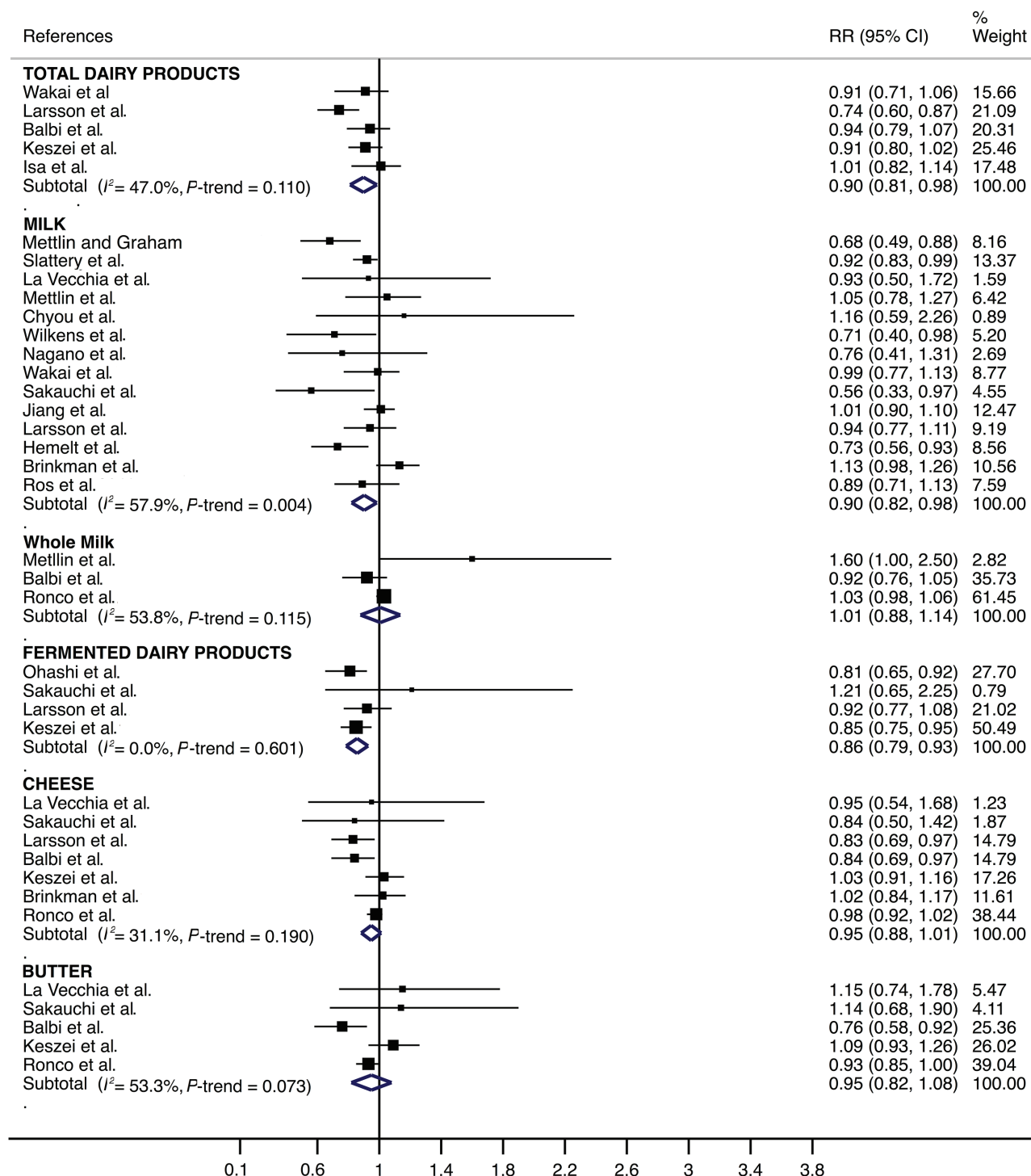


FIGURE 2 Forest plot including risk ratio of medium compared with low dairy product intake for bladder cancer in the adult population.

to perform an analysis of milk consumption only. The risk of bladder cancer associated with medium compared with low consumption was significantly protective in the Asian region (RR = 0.79; 95% CI: 0.59, 0.98, $I^2 = 56.8\%$) and for the cohort design studies (RR = 0.85; 95% CI: 0.71, 0.99, $I^2 = 19.7\%$) (Table 3).

The random-effects meta-regression model could be performed only for milk consumption, showing that the age of participants ($P = 0.744$ for high compared with low and $P = 0.442$ for medium compared with low), percentage of current smokers ($P = 0.841$ for high compared with low and $P = 0.078$ for medium compared with low), and the

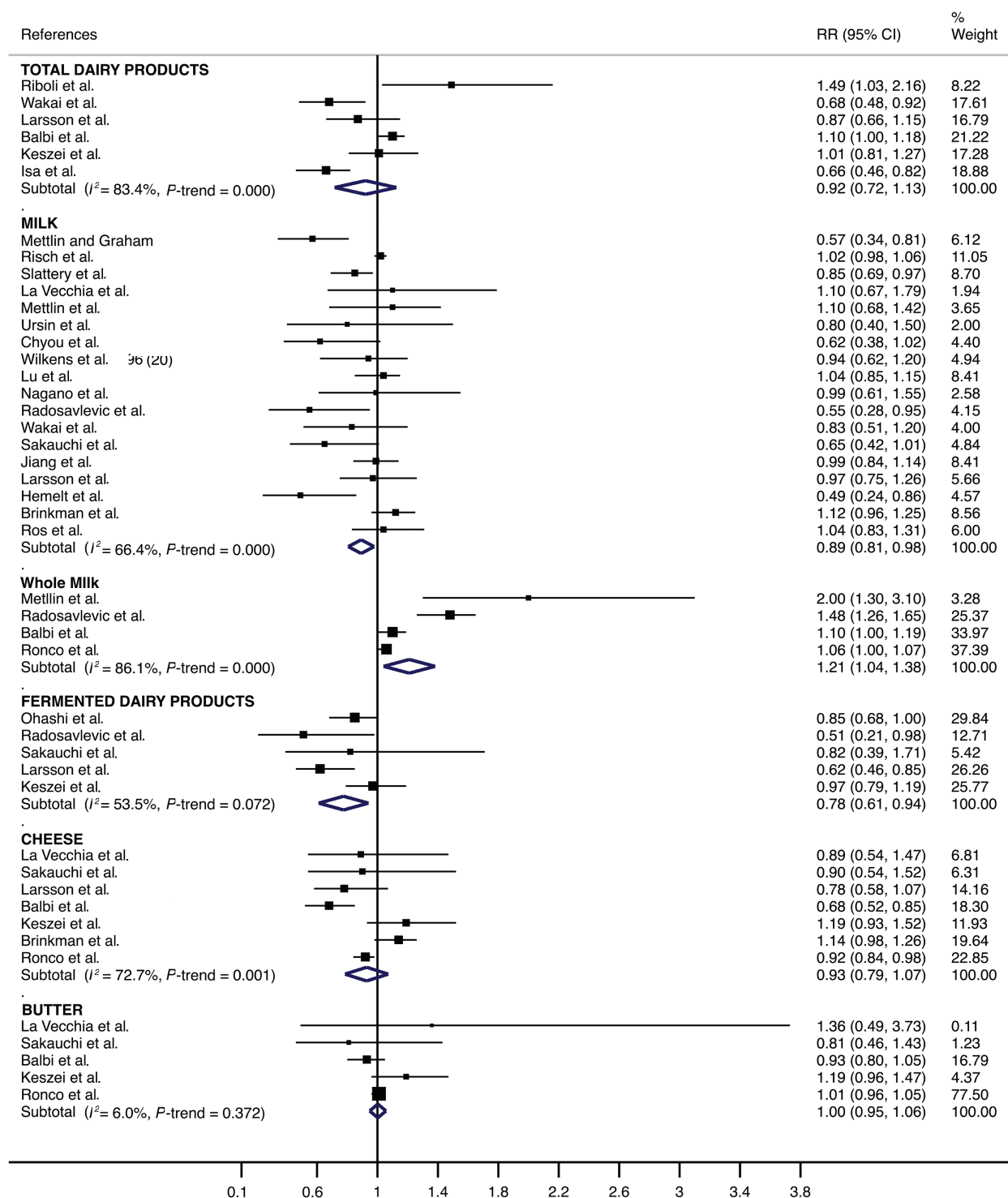


FIGURE 3 Forest plot including risk ratio of high compared with low dairy product intake for bladder cancer in the adult population.

year when the study started ($P = 0.218$ for high compared with low and $P = 0.353$ for medium compared with low) were not related to the pooled RR estimates (Figures 4 and 5).

Publication bias

Publication bias was analyzed for only milk consumption because ≥ 10 articles addressing milk were included in this systematic review and meta-analysis. Evidence of publication

TABLE 3 Subgroup analyses for the risk of bladder cancer for high compared with low and medium compared with low milk intake in the adult population, based on gender, region, and type of study design¹

Subgroup	<i>n</i>	High vs. low consumption RR (95% CI)	<i>I</i> ²	<i>P</i>	Medium vs. low consumption RR (95% CI)	<i>I</i> ²	<i>P</i>
Gender							
Male	4	0.86 (0.65, 1.07)	78.7	0.003	0.93 (0.77, 1.08)	34.6	0.217
Female	3	0.97 (0.85, 1.08)	68.2	0.043	—	—	—
Geographical location							
Americas	7	0.88 (0.76, 1.01)	74.9	0.001	0.90 (0.79, 1.02)	59.2	0.031
Europe	6	0.96 (0.79, 1.13)	51.2	0.068	1.00 (0.87, 1.13)	37.2	0.189
Asia	5	0.80 (0.57, 1.04)	69.4	0.011	0.79 (0.59, 0.98)	56.8	0.074
Type of design							
Case-control	12	0.90 (0.80, 1.01)	72.4	<0.001	0.92 (0.82, 1.02)	67.3	0.002
Cohort	6	0.86 (0.70, 1.02)	31.6	0.199	0.85 (0.71, 0.99)	19.7	0.289

¹*P* < 0.05 indicates the presence of heterogeneity between studies.

bias was found by funnel plot asymmetry and Egger's test for only high compared with low milk consumption (*P* = 0.020) (Figure 6).

Discussion

The present meta-analysis summarized the evidence to date regarding the association between milk and dairy product consumption and bladder cancer risk, representing a pooled total of 26 epidemiologic studies (8 cohort and 18 case-control) with a total sample size of ≤595,698 to obtain more stable results. The study results suggested that medium compared with low consumption of total dairy products, milk, and fermented milk decreased the risk of bladder cancer. Moreover, high compared with low consumption of milk and fermented milk products also decreased the risk. In contrast, high compared with low consumption of whole milk was significantly associated with a higher risk of bladder cancer. No association was observed with butter and cheese consumption or with high compared with low consumption of any other type of dairy products.

The results of medium fermented milk consumption demonstrated no heterogeneity. However, as in both previous meta-analyses (5,6), considerable heterogeneity was detected in the other significant results, especially in whole milk, for which heterogeneity was substantial. Different factors could influence the heterogeneity, including age, gender, geographic location, type of design, smoking, and year when the study started. Most studies included in the present meta-analysis adjusted the results by ≥3 of the most important factors. Moreover, based on the subgroup analyses by gender, geographic location, and type of study design, the present meta-analysis indicated that a significant proportion of the observed heterogeneity in the milk results may be explained by differences in study location and study design. In addition, the random-effects meta-regression model showed that the age of the participants, the percentage of current smokers, and the year when the study started were not related to the pooled RR estimates. Furthermore, the sensitivity analysis showed that the significantly lower risk of bladder cancer associated with medium compared with low milk

consumption disappeared with the removal of 3 studies. Finally, publication bias was found for milk consumption. Therefore, the results should be interpreted with caution.

In spite of the heterogeneity and the risk of bias detected in the present meta-analysis, 3 important aspects warrant further discussion.

First, the results showed that the relation between consumption of milk and dairy products and bladder cancer risk varied significantly by the type of dairy product. The present meta-analysis observed a decrease in the risk of bladder cancer associated with medium consumption of total dairy products and with medium and high consumption of milk and fermented dairy products but no associations with cheese or butter consumption. Of the previous meta-analyses, Mao et al. (6) suggested a potential protective effect of high milk consumption for bladder cancer and Li et al. (5) only observed an inverse association in the United States for bladder cancer risk and high milk consumption, and in Japan for bladder cancer risk and high total dairy product consumption with a limited study population. Several biological mechanisms have been proposed in order to explain the relation between milk and dairy product consumption and bladder cancer risk. Milk and dairy products contain several bioactive constituents that are potentially protective against cancer, one of which is vitamin D. Although they do not contain vitamin D naturally, enriched/fortified milk and dairy products can constitute a significant source of vitamin D (41). Vitamin D not only impedes proliferation and induces apoptosis in tumor cells but also regulates metabolism-related tumor suppressors and oncogenes (42). In this regard, an association between vitamin D deficiency status and increased risk of bladder cancer has been observed (43). Indeed, the latest related meta-analyses have demonstrated that maintaining sufficient serum 25-hydroxyvitamin D concentrations is associated with decreased bladder cancer risk (44, 45). However, the observational studies included in the present meta-analysis do not specify whether the dairy products they registered were fortified with vitamin D. Other bioactive compounds present in milk and dairy products, such as calcium (46, 47), casein, and lactose as promoters of calcium bioavailability (48) and vitamin A (49), have

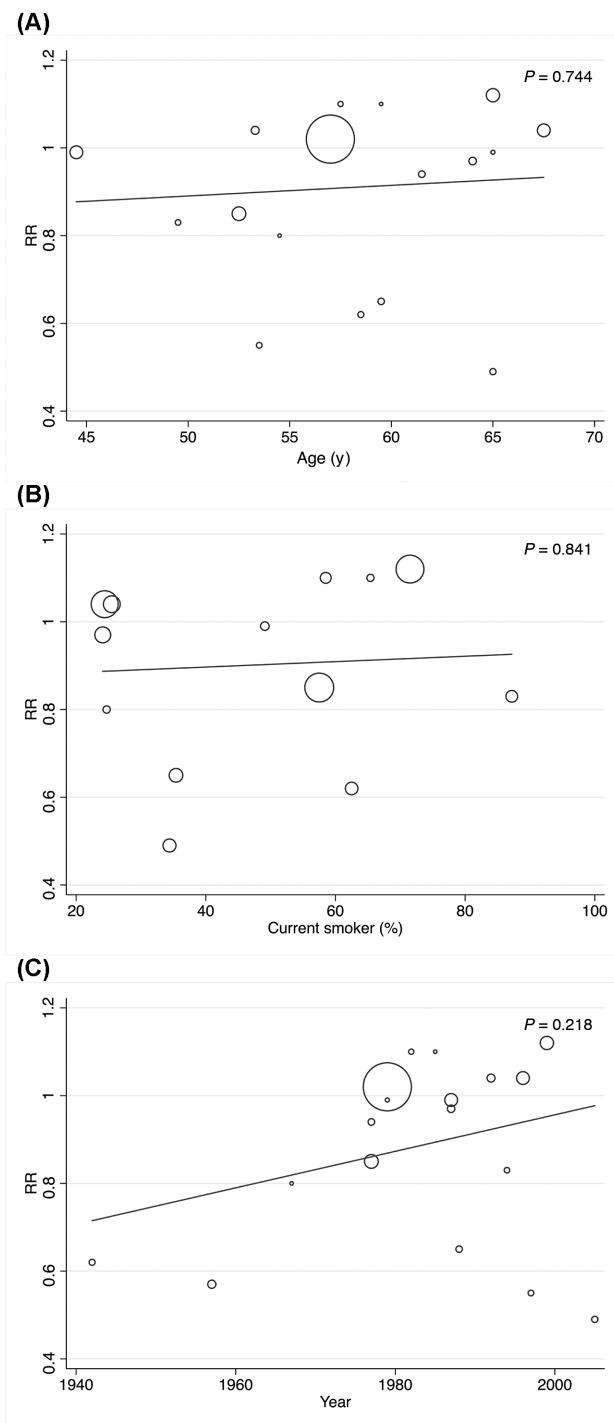


FIGURE 4 Random-effects meta-regression analyses for the moderator effect of age, current smoker, and the year of beginning of the studies in the relation between high compared with low milk intake and bladder cancer in the adult population.

also been related with a decreased risk of some kinds of cancers.

Nevertheless, the prognostic factor measurement of the primary studies included in the present meta-analysis did not allow us to obtain data about nutrient intakes, so it was not possible to establish an association to support

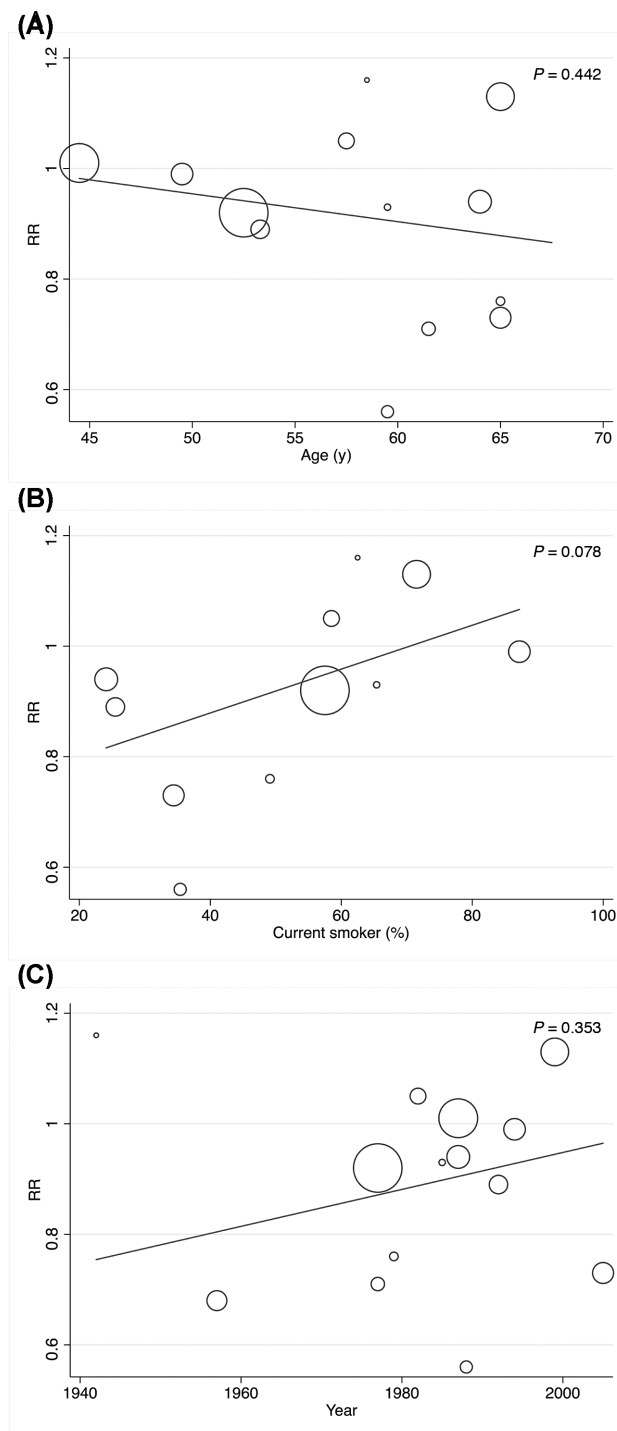


FIGURE 5 Random-effects meta-regression analyses for the moderator effect of age, current smoker, and the year of beginning of the studies in the relation between medium compared with low milk intake and bladder cancer in the adult population.

the contribution of dairy products to the previous biological mechanism described. In addition to the bioactive compounds, fermented dairy products contain probiotics, live microorganisms whose beneficial effects for human health have been widely described (50). The mechanism of action of probiotic microorganisms can be explained by

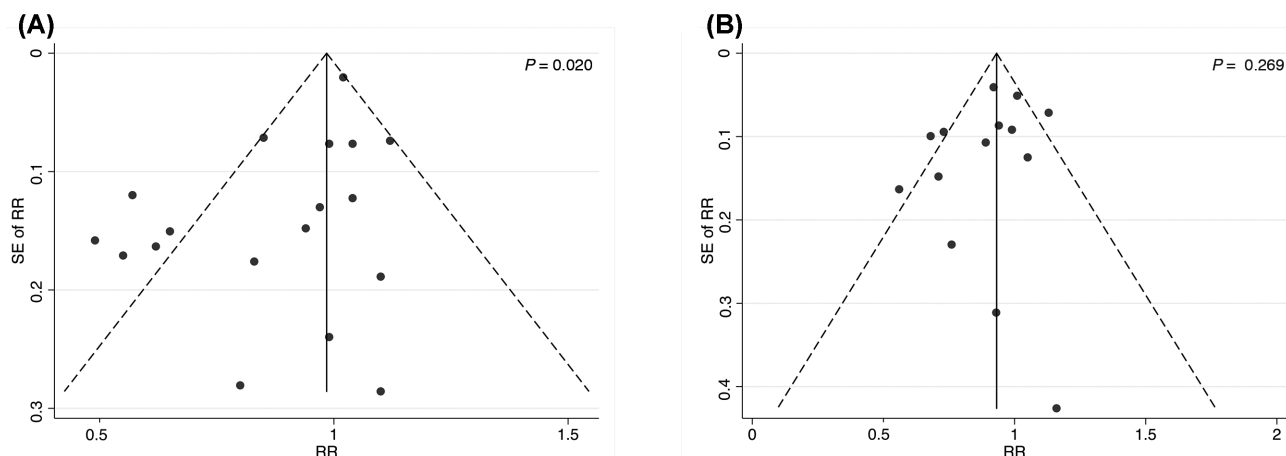


FIGURE 6 Assessment of potential publication bias by Egger test for studies addressing the relation between high compared with low and medium compared with low milk intake and bladder cancer in the adult population.

the enhancement of the nonspecific and specific immune responses of the host, production of antimicrobial substances, and competition with pathogens for binding sites (51). To date, no evidence has been generated about the possible relation of fermented dairy product consumption with the risk of bladder cancer. However, probiotics have shown a suppressing effect on superficial bladder cancer (52). Moreover, in a prospective study of a Swedish adult population, it was observed that a high intake of fermented milk may lower the risk of developing bladder cancer (38). In this regard, it has been observed that probiotics are capable of altering host immune function, conferring protection from localized and excessive inflammatory responses (53), and improving rates of bladder cancer recurrence (54). In addition, some studies have supported the hypothesis that habitual consumption of lactic acid bacteria can promote anticancer immunity (24).

The second important result relates to the fat content in milk. According with the results observed by Mao et al. (6), in the current study high whole milk consumption seemed to increase the risk of developing bladder cancer. Nevertheless, the heterogeneity in these data was substantial, and this result should be considered with caution. Moreover, other fatty dairy products, such as cheese and butter, did not present this adverse association. Total fat intake has been related to bladder cancer risk (55). The main hypothesis supporting a possible effect of fat on cancer risk is based on the intraluminal effect of products of fat digestion, such as secondary bile acids; however, human data supporting this hypothesis are weak (56). In this regard, milk and dairy products are an important dietary source of total and saturated fats (57). Indeed, the main portion of milk lipids (97–98%) is TGs or esters of fatty acids (58). Nevertheless, milk fat also contains conjugated linoleic acid (CLA), a geometrical and positional stereoisomer of linoleic acid, which is present in milk and dairy products and derived from ruminants (59). It has been observed that CLA exerts

antineoplastic activity and may have antiproliferative or proapoptotic properties. Indeed, a strong inhibition by CLA of malignant bladder cancer cell lines has been observed (60). This is possible mainly because CLA, with its t10c12 isomer, inhibits insulin-like growth factor receptor (IGF-IR) signaling, which contributes to decreased cell proliferation and increased apoptosis of cancerous bladder cells (61). Indeed, whole milk consumption has been associated with a decreased risk of some cancers, such as prostate cancer. In contrast, total milk and low-fat milk have been related to higher risk of prostate cancer (62). The diverging results for fat in dairy products suggest that further studies are needed to clarify the influence of fat content on bladder cancer risk. Currently, the recommendation provided by some of the most important institutions in the field of nutrition is that low-fat dairy varieties should be encouraged (63, 64).

The last highlighted issue indicated that the quantity of dairy products consumed might play an important role in their relation with bladder cancer risk. To date, the meta-analyses published to evaluate the relation between milk and dairy products and bladder cancer have measured the highest compared with the lowest quantiles of consumption (5, 6). To our knowledge, this is the first meta-analysis to evaluate not only high compared with low consumption but also medium compared with low consumption. The present study observed a reduced risk of bladder cancer with medium consumption of total dairy products, milk, and fermented products and with high consumption of milk and fermented products. In contrast, Mao et al. (6) observed only high compared with low milk consumption was significantly associated with a reduced risk of bladder cancer and Li et al. (5) only observed an inverse association in the United States for bladder cancer risk and high milk consumption, and in Japan for bladder cancer risk and high total dairy product consumption with a limited study population. In the current meta-analysis, it was not possible to carry out a dose–response analysis. To elucidate the amounts

of milk and total dairy product consumption that were included in the low, medium, or high categories, approximate mean values were calculated. These data indicated that the medium consumption of milk (~227 mL/d) and total dairy products (~345 g/d) was similar to the minimum servings recommended in the most important food guides (64, 65). For example, The “Dietary Guidelines for Americans” issued by the USDA and US Department of Health and Human Services recommends 3 servings from the “milk, yogurt and cheese” food group each day as part of a healthy, balanced diet. Examples of 1 serving include 200 mL of milk, 125 g of yogurt, or 25 g of hard cheese (64), so the minimum serving recommended for total dairy products, including “milk, yogurt and cheese,” is 350 g/d. Therefore, in regards to the results of the present meta-analysis, the combination of a serving of milk and fermented dairy products might be a suitable option to obtain benefits related to decreased bladder cancer risk. However, in the subgroup analysis of milk consumption by geographical location, a reduction in bladder cancer risk was observed for medium consumption only in the Asia region. The approximate mean calculated in the Asia population was lower than in America or Europe, so the results reported in the present study may require us to reflect on the adequate daily recommendation for milk. Nevertheless, additional factors related to the Asian population also need to be taken into account, such as the possible role of their healthy dietary and lifestyle habits and other genetic differences (66). For example, lactose intolerance occurs in ~25% of people in Europe; 50–80% of people of Hispanic origin, people from south India, and black people; and almost 100% of people in Asia (67).

Finally, in relation to dairy products, it is important to highlight that milk consumption in developed countries has been declining slightly in the last few decades. A recent update from the USDA (68) confirmed that dairy milk consumption declined 25% from 1996 to 2016 (68). This observed reduction in consumption of milk may be a result of campaigns promoting the idea of cow milk consumption being unsuitable for humans (69). In recent years, influential groups have criticized milk and dairy products and recommend limiting consumption of dairy-based foods due to little benefit and potential harm to humans (70, 71). However, the available scientific evidence supports the intake of milk and dairy products contributing to meeting nutrient recommendations and that it may protect against the most prevalent chronic diseases and the risk of all-cause mortality, whereas very few adverse effects have been reported (72–74). The results of the present meta-analysis contribute to broadening this evidence.

As a systematic review and meta-analysis of previously published studies, our study has several limitations that need to be taken into account when considering its contributions. First, because both case-control and cohort studies were included, a wide variation exists across studies and the methodological differences in the study designs could bias the results because of the great variety included in the analysis. In addition, the results of total milk and dairy product

intake were based on responses to a single questionnaire that was administered only once. A second limitation is that heterogeneity may be due to milk and dairy product intakes including a collection of several products and reported dairy items which may have varied across studies and some items were combined. Lastly, other important dietary and lifestyle factors may have influenced the results because they were not considered in most of the primary studies included. Therefore, these results should be interpreted with caution.

In conclusion, the results of the present meta-analysis suggest a decreased risk of bladder cancer associated with medium consumption of total dairy products (~345 g/d) and with medium and high consumption of milk (~227 mL/d, ~336 mL/d) and fermented dairy products (~67 g/d, ~160 g/d). Moreover, an increased risk of bladder cancer was observed with high whole milk consumption (~220 mL/d), although the results should be interpreted with caution. Currently, the intake of milk and dairy products should follow the dietary recommendations put forth by the competent authorities of each country. The daily combination of milk and fermented dairy products might be a healthy option to reduce bladder cancer risk. Future research is warranted to clarify the adequate serving size and the role of fat content and the different geographical locations to establish conclusive recommendations for reducing the risk of bladder cancer.

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